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Multi-color MPI for distinguishing two different MNP systems after cellular uptake

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Abstract

To demonstrate the capability of multi-color magnetic particle imaging (MPI) to distinguish different magnetic nanoparticle (MNP) systems after cellular uptake, we investigated two distinct MNP samples after cellular uptake by THP 1 monocytes. Magnetic particle spectroscopy (MPS) and MPI were employed to characterize the unique magnetic signatures of each MNP-labeled cell sample, allowing for clear differentiation. These findings establish the basis for future applications in tracking specific monocyte subpopulations, thereby enabling detailed investigation of immune cell functions and migration patterns within inflammatory processes.

I. Introduction

Tracking specific cell populations is crucial for biomedical research, particularly in studying immune responses and inflammatory diseases. Human monocytes can be categorized into distinct subpopulations based on specific surface markers such as CD14 and CD16. Each subpopulation plays a unique functional role in the immune response, contributing to processes such as inflammation, tissue repair, and pathogen clearance [1]. Only a limited number of imaging modalities are capable of accurately tracking different cell types simultaneously [2]. Magnetic Particle Imaging (MPI), a non-invasive, radiation-free imaging technique specifically sensitive to magnetic nanoparticles (MNPs), has emerged as a valuable tool for cell tracking applications [3,4]. In this study, we demonstrate the feasibility of using multi-color MPI to distinguish between cell populations involved in inflammation. Specifically, we show that multi-color MPI can clearly differentiate between two distinct types of MNPs after cellular uptake.

II. Methods and materials

II.I. Magnetic Nanoparticles (MNPs)

We used Synomag (LOT: 12121103-01, 30 nm diameter) with a citrate surface, referred to as C30, and Synomag prior coating (LOT: 03922103-01, 50 nm diameter), referred to as P50, both obtained from micromod Partikeltechnologie GmbH (GER).

II.II. Cell line

The experiments were performed with human tumor cells (THP-1 monocytes), purchased from ATCC® (GER). The cells were cultured in Roswell Park Memorial Institute 1640 medium (Invitrogen, GER) with 10% fetal calf serum (Biochrom, GER) and 1% penicillin-streptomycin (Invitrogen, GER) at 37°C and 5% CO_2. For all measurements 5×10^6 cells were labeled with MNPs at an iron concentration of $c(\mathrm{Fe}) = 0.5$ mmol/L for 10 minutes, using phosphate-buffered saline (PBS) (Gibco, GER) to dilute the MNPs as described in [5]. Our previous studies have shown that C30 MNPs have a cellular uptake of 5(1) pg

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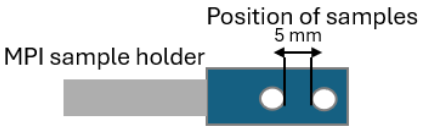

Figure 1: Setup of the multi-color MPI showing the MPI sample holder and PCR tubes positioned 5 mm apart.

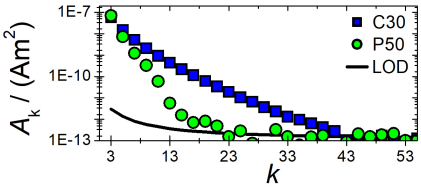

Figure 2: Amplitude spectrum of P50-labeled cells (green) and C30-labeled cells (blue).

per cell, while P50 MNPs bind to the cell surface with 20(3) pg per cell [3].

II.III. Magnetic particle spectroscopy (MPS)

In MPS, a sinusoidal excitation field of an amplitude B at frequency f_0 is applied to an MNP sample. Due to the non-linear magnetization of MNPs, the response is decomposed by Fourier transform (FT) into odd multiples of f_0 (higher harmonics A_i). The third amplitude A_3 is used for MNP quantification, as it carries the highest signal, while the first harmonic is filtered out. To assess the MPI performance, the number of amplitudes (A_k) above the detection limit (LOD) k_{LOD} is determined. The LOD is defined as $\mu + 3\sigma$, where μ is the mean and σ the standard deviation of ten background measurements.

II.IV. Magnetic particle imaging (MPI)

MPI measurements were conducted using a preclinical MPI scanner (Bruker MPI 25/50 FF, GER) that generates a field-free-point (FFP). The FFP is moved covering a field of view (FOV) and from the induced time signal of the coil the harmonic spectrum is derived by FT. The image reconstruction of the MNP distribution is performed by solving an inverse problem, which requires the system function (SF). The SF acquisition took 9 h. Multi-color MPI allows differentiation of superimposed signal contributions, such as those from distinct MNP states, within the same measurement. This is achieved by recording SFs specific to these MNP states, which were subsequently employed for image reconstruction. For this, two tubes (Thermo Fisher Scientific, GER) containing MNP-labeled cells (volume = 27 µL) were positioned 5 mm apart on the MPI sample holder, see Fig. 1.

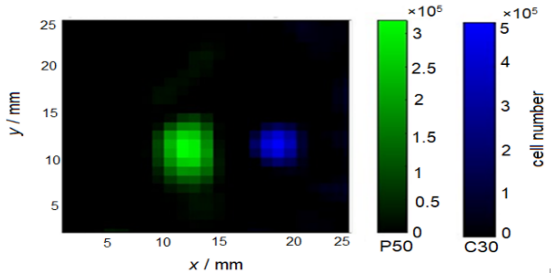

Figure 3: Multi-color MPI of C30-labeled cells (blue) compared to P50-labeled cells (green).

III. Results and discussion

III.I. MPS characterization of C30 and P50

In Figure 2, the amplitude spectrum A_k normalized to the third amplitude A_3 is shown as a function of harmonics k for cells labeled with C30 (blue) and P50 (green). The black line marks the LOD ($A_{3,LOD}$=310^{-12} Am^2). C30 shows higher signal amplitudes compared to P50. Specifically, the C30-labeled cells have a k_{LOD} of 41, whereas the P50-labeled cells exhibit a k_{LOD} of 21.

III.II. Multi-color MPI of C30 and P50

Figure 3 shows multi-color MPI results distinguishing C30-labeled cells (blue) from P50-labeled cells (green). P50-labeled cells exhibit a more blurred image and lower resolution compared to C30-labeled cells, despite the higher binding of P50, due to the twice lower k_{LOD}.

IV. Conclusions

We demonstrated the potential of multi-color MPI for distinguishing different MNP systems after cellular uptake based on their unique magnetic properties. The next step is labeling distinct cell populations with MNPs in preclinical models to study cell behavior and interactions in a physiological context, improving our understanding of immunological processes.

Acknowledgments

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Author's statement

Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration and has been approved by the authors' institutional review board or equivalent committee.

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